

Surveillance of Microcephaly – Webinar Transcript
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Presenter: Janet D. Cragan, MD, MPH
Birth Defects Branch, NCBDDD, CDC

Slide Number	Text
Slide 1: Introduction	This is Jan Cragan from the National Center on Birth Defects and Developmental Disabilities at CDC. This webinar is going to talk about conducting surveillance for microcephaly. It's going to cover all types of microcephaly, all causes. I will speak a little bit about Zika virus in relation to microcephaly, but only a little bit. The seminar will cover microcephaly in general.
Slide 2: Outline	First, I'll talk about what microcephaly is, and the surveillance definition for microcephaly. Then [I'll] go over the different causes of this defect. We'll talk about case ascertainment, what information needs to be collected for conducting surveillance, and then a little bit about how to estimate prevalence and monitoring for changes in prevalence.
Slide 3: Microcephaly	Microcephaly is actually a clinical finding it's not a diagnosis by itself. It's the finding of a small head [when] compared with infants of the same sex and age or the same gestational age. The head circumference is considered a reliable estimate of the volume of the underlying brain. Head circumference is also known as occipital-frontal circumference or OFC. And in the diagrams you can see a baby with a normal head size, one that has some degree of microcephaly where the head is smaller, and then a baby with very severe microcephaly.
Slide 4: Congenital Microcephaly	Congenital microcephaly is present either prenatally or at the time of birth or delivery. It can develop from abnormal development of the brain - basically from the beginning - which can be genetic in origin, or it can result from arrest or destruction of a brain that previously was forming normally. So, for instance, if there's an <i>in utero</i> infection or vascular disruption that impacts the brain then the growth can be abnormal subsequently. Acquired microcephaly develops after birth due to a delivery complication or a post-natal insult, such as trauma or infection. In this instance the head circumference is normal at birth but as the baby grows in length the head circumference becomes comparatively smaller.
Slide 5: Types of Microcephaly	<p>There are actually several different types of microcephaly. Disproportionate microcephaly is when the head is small out of proportion to the weight and length, which may be normal for age and sex. Proportionate microcephaly is when the head size, the weight, and the length all are small for age and sex, but they are proportional to each other. "Relative" microcephaly can be seen in some medical records and it generally refers to a head size that measures within the normal range for age and sex, but it's small out of proportion to the weight and the length of the baby.</p> <p>Microcephaly can be diagnosed prenatally. It can be detected on mid-pregnancy anomaly scans at about eighteen to twenty weeks, but not always. In some instances it may not be evident until late in the second or even into the third trimester. It's usually present in most cases by thirty six weeks gestation. So, if you detect microcephaly on a mid-pregnancy scan then that's one thing. If you don't see it on a mid-pregnancy scan it doesn't necessarily mean that it won't be evident or developing later. And so, often serial prenatal ultrasounds are needed to detect the development of microcephaly <i>in utero</i>.</p>
Slide 6: Other Birth Defects With Abnormal Head Size	There are other birth defects that can result in a small head size, or microcephaly, due to the process of their formation and this is not really considered true microcephaly. This is a small head as a feature of another defect. So, anencephaly is an example of this where there's failure of the neural tube to close that results in failure of the brain and the skull to

	<p>form. So, it isn't that the brain or the head are small, it's that they actually didn't develop. You can sometimes see microcephaly with spina bifida. This is another type of neural tube defect where there's failure of the tube closure that results in an opening in the spine and that can occur anywhere along the spine. [In these infants] Sometimes the head will be normal size, sometimes it will be large, but sometimes it can be small as well, and those infants may at some point be referred to as having microcephaly.</p>
Slide 7: Other Birth Defects With Abnormal Head Size – Continued	<p>An encephalocele is a sac like protrusion of the brain or the membranes from an opening in the skull, and those infants can have other types of brain and facial defects associated with it. But, again, the head circumference may be small but it's due to the encephalocele not just microcephaly. Holoprosencephaly is a failure of the brain to fully divide into two cerebral hemispheres - into two parts - and these children often can have a small head as well. But the diagnosis is not microcephaly, the diagnosis is the holoprosencephaly. And then another term that can be found in many records is hydrocephalus and this is accumulation of fluid in the brain. It typically results in enlarged ventricles, and sometimes can result in an enlarged head and head size as well. Not a small size but a large [head].</p>
Slide 8: Brain Abnormalities That Can Occur with Congenital Microcephaly	<p>There are also brain abnormalities that can occur as part of the microcephaly. So, these infants can have intracranial calcifications - areas of calcium within the brain substance - and that is seen often with <i>in utero</i> infections although it can result from other things. There's a condition called hydrocephalus ex-vacuo, which is not the same thing as typical hydrocephalus, but this is where the brain has been damaged so much that it actually shrinks and is then surrounded by extra fluid within the skull. Hydranencephaly is where the damaged brain matter is replaced by pockets of fluid, so you'll see areas of fluid within the substance of the brain. And then you can have pachygyria, or what's known as lissencephaly, where there are abnormal ridges and folds - or gyri - in the brain. The brain may not have as many folds as you would normally see on the exterior surface, and all of these things can be seen in an infant with microcephaly.</p>
Slide 9: Measuring Head Circumference (WHO*)	<p>So, an important consideration is how head circumference is measured because it isn't always as simple as it sounds. These are guidelines from the World Health Organization. They suggest using a measuring tape that cannot be stretched. What you do is you securely wrap the tape around the widest possible circumference of the head, and that's usually one to two finger widths above the eyebrow on the forehead, and then across the most prominent part of the back of the head as you can see in the drawing there. It's recommended that you take the measurements three times and select the largest to the nearest 0.1 centimeter. The optimal time to measure head circumference is at about twenty four to thirty six hours after birth. There can be significant molding of the skull and the head shape during delivery through the birth canal, and it takes a few hours for that to settle and [for] the head to regain its primary shape. So optimally it's best to record after a day or so has gone by. However, I think in most hospitals in the US head circumference measurements are taken very soon after birth.</p>
Slide 10: Measuring Head Circumference	<p>This shows the tape measure around the heads of the babies in that same drawing [referring to Slide 3: Microcephaly]. The baby with the typical normal head size, a baby with microcephaly, and a baby with severe microcephaly, and you can see how it may be difficult to find what's the widest circumference of the head. Where do you place the tape when the head is small? Maybe it slips while you're measuring - so the measurements can vary somewhat just due to the difficulties in taking them.</p>
Slide 11: Definition of Congenital Microcephaly	<p>So, for the purposes of surveillance and many of the studies that look at microcephaly, the case definition is the following:</p> <p>Definite microcephaly in live births is defined as the head circumference at birth - at the time of delivery or within the first day or two - that's less than the third percentile for the</p>

	<p>child's gestational age and sex. Or, if there's not a head circumference available at the time of birth, then a head circumference less than third percentile for age and sex within the first six weeks of life - and that's adjusted for gestational age if it's a pre-term infant. For stillbirths and elective terminations, the head circumference at delivery would be less than third percentile for gestational age and sex.</p> <p>Possible microcephaly is defined in a live birth as the setting where a head circumference is not available before six weeks of life, but the head circumference beyond six weeks of life is less than third percentile for age and sex. So, you don't have a measurement from birth or soon after birth but the child has a very small head at a later time. That could be congenital microcephaly, but it also potentially could be acquired microcephaly. So it's listed as a possible case. For all pregnancy outcomes, if microcephaly is diagnosed or suspected on a prenatal ultrasound but there are no available post-natal head circumference measurements then that would be considered possible microcephaly. Particularly with still born infants and pregnancies that are electively terminated after prenatal diagnosis of a defect, there may not be a post-natal head circumference measurement performed.</p>
Slide 12: Definition of Congenital Microcephaly	<p>Those are our case definitions. In reality, there really is no single universally accepted definition of congenital microcephaly. Different clinicians use different cut-off points for different purposes. Some may consider less than fifth percentile or even less than tenth percentile for age and sex as microcephaly or at least a small head size that needs further follow-up. We suggest that these children be included in surveillance data because they carry a diagnosis of microcephaly. But programs need to obtain the relevant head circumference measurements, along with the date, and the child's age when they were recorded - if they're available in the medical records - so that you can look at where the child actually falls in measurements of the head circumference both at birth and as the child grows.</p> <p>Children for whom no head circumference measurement is available in the medical record, but it states that they have congenital microcephaly, we recommend those be included in surveillance data as well because they carry the diagnosis. But as you'll see later, we'll look at them a little bit differently. It's important that surveillance staff not assign a diagnosis of microcephaly based only on a head circumference value in the medical record without mention of the clinical diagnosis by a physician. As we said, head circumference measurements are often difficult to do accurately, particularly if a baby is fussy and crying and active, and so we do not recommend assigning the diagnosis just based just on a measurement without some clinical reference to the condition being present.</p>
Slide 13: Suggested Reference Charts for Head Circumference At Birth by Gestational Age	<p>So, the next slide has some suggested reference charts for head circumference measurements at birth, where you plot out the corresponding percentile related to the child's sex and gestational age. These are references just for birth measurements, not older children but just at birth. The INTERGROWTH-21st website has standard charts for newborns thirty three weeks through full term, and also charts for very pre-term infants twenty four weeks to thirty two weeks gestation. And we recommend those as good reference charts to plot these figures. Both have a tool also available from the website where you can enter the gestational age and the head circumference measurement and it will give you what the percentile value is.</p> <p>The website also has intrauterine head measurements for fetal growth less than twenty four weeks, and these are available as references. In reality there really aren't any international standards for birth measurements in infants less than twenty four weeks and measurements <i>in utero</i> actually are thought to under estimate the actual head</p>

	<p>circumference measurement at birth. So, it's difficult to have standards for less than twenty four weeks gestation. And in reality, many of those pregnancies are going to end in fetal death or in elective termination, and so measurements may not be taken at all. So, really in those very early gestational age pregnancies we recommend a clinician review the records, review the prenatal diagnosis, and what's done postnatally, and make a clinical determination of whether it really constitutes conclusive microcephaly.</p>
Slide 14: Additional Resources for Growth Charts	<p>I've also included a few additional resources for other types of growth charts. We recommend the INTERGROWTH-21st charts because they were taken from populations around the world that had similar factors in terms of nutrition, and availability of healthcare, and such. But there are some other tools available out there as well. For infants who are beyond the birth period and are growing, the World Health Organization has child growth standards from birth to five years of age available on their website, and these are fine to use for term infants. And then the INTERGROWTH-21st website also has separate charts for postnatal growth standards for preterm infants. So infants who are preterm and then are growing subsequently, you can plot head circumference measurements there as well.</p>
Slide 15: Fetal Brain Disruption Sequence	<p>So, there's an interesting malformation known as the fetal brain disruption sequence that has been seen in a number of the infants in Brazil that have been born with microcephaly, and this is a very unusual and very rare defect. It was first described in 1984, but it had been noted in the literature prior to that. Basically, what happens is the brain is severely malformed - there's a disruption and - because the brain doesn't grow the fetal skull collapses in. This all happens <i>in utero</i>, and the skull collapses in on the brain and you get microcephaly. But you also get rugae or folds, excess folds, in the scalp - the skin covering the head - because the skull has collapsed. And you can see, on the X-ray, you can actually see where the skull bones collapsed onto each other. And this is a very unusual phenotype of brain destruction <i>in utero</i> but it has been described in some of the infants in Brazil.</p>
Slide 16: Causes of Microcephaly That is Present at Birth	<p>So, there are a number of causes of congenital microcephaly. There are known infections that can result in microcephaly and these include <i>in utero</i> toxoplasmosis, congenital rubella, cytomegalovirus, herpes infection <i>in utero</i>, HIV, and congenital syphilis. And, of course the question now is should Zika virus be added to that list.</p>
Slide 17: Causes of Microcephaly That is Present at Birth – Continued	<p>There are also genetic causes of microcephaly, and we don't really know how many instances of just isolated microcephaly have their origins in genetics. But there are some single gene disorders or syndromes where microcephaly is a feature. There are chromosomal abnormalities - trisomy 21 or Down syndrome is one of them - microdeletions and micro duplications, where microcephaly can be seen in association, as well as mitochondrial mutations.</p> <p>Microcephaly can also result from <i>in utero</i> ischemia or hypoxia which you might see in terms of placental insufficiency or a placental abruption where the oxygen supply and the blood supply to the fetus is compromised and the brain may not grow as well. There are a few teratogens that are known to cause microcephaly. Maternal alcohol use is one. Microcephaly is a feature of fetal alcohol syndrome. And then hydantoin, which is an anti-epileptic drug, is also known to cause this when taken by the mother. Radiation exposure in significant amounts can result in microcephaly, as can mercury ingestion which is usually through eating fish and seafood that contain high content of mercury. And then there are some maternal conditions and complications that can lead to microcephaly and these can include poorly controlled diabetes in the mother, or hyperphenylalaninemia.</p>
Slide 18: Goals of Microcephaly Surveillance	<p>So, when you're conducting surveillance for microcephaly, the goals are really to identify all the infants in the population that have been diagnosed with congenital microcephaly that's present at birth or at delivery. You want to estimate the prevalence of congenital</p>

	<p>microcephaly over recent years to determine a baseline for how often this condition occurs in your population. And then you want to be able to monitor the frequency of congenital microcephaly going forward to assess increases that might reflect Zika virus infection during pregnancy or other types of causes.</p>
<p>Slide 19: Ascertainment Sources</p>	<p>So, the sources where you might identify infants with microcephaly include the following: First, certainly wherever deliveries occur because most instances of significant microcephaly where the head circumference is less than third percentile is going to be pretty evident clinically right after delivery. So birth hospitals, birthing centers, or midwifery practices. And you also need to look at how often do home births occur in your population. And then the other question is where are elective terminations performed after prenatal diagnosis of a defect because if the brain is severely affected, some pregnancies may result in termination and you need to know where those are being conducted.</p> <p>[You] also need to find out whether the information is available on vital records. The US standard birth certificate does not include a field for head circumference, but there are a couple of states where it is included. Massachusetts is one of them, and I know there are other states that are considering including this as a way to monitor for microcephaly in the population.</p> <p>And then you need to look at where children with microcephaly are seen and evaluated, and that would be certainly pediatricians and family practitioners but also in sub-specialty clinics - pediatric neurology clinics, genetics clinics, and then developmental clinics, and early intervention programs where children with brain damage may be evaluated.</p> <p>And then you need to look at what kind of reporting you can get from healthcare providers, and state programs. And particularly for surveillance going forward it's important to be sure that you revise reporting forms to include all of the information that you want to know about microcephaly.</p>
<p>Slide 20: Ascertainment Sources – Continued</p>	<p>One of the concerns is whether your data sources will be able to identify infants retrospectively with microcephaly. So trying to get a baseline of how often it happens among children born in recent years, you need to know whether data sources can go back and find those children. There is both an ICD-9-CM and ICD-10CM code specific to microcephaly.</p> <p>You may need to educate the healthcare community about microcephaly and why reporting it is important - the importance of measuring and recording the head circumference for every child born in every setting. And increasing awareness, and being aware that increased awareness and reporting alone may increase the observed prevalence that you see so, you need to factor that in. And then it's probably important to provide feedback and ongoing updates of what's being seen in the population to maintain high levels of reporting and ascertainment going forward.</p>
<p>Slide 21: Information to Collect</p>	<p>So, the information that needs to be collected:</p> <p>Certainly you need to be able to identify the children, the parents, the physicians, so that you can follow up with affected children over time and assess where the cases are occurring - where these mothers lived at the time of delivery for example. Important maternal information includes dates of the last menstrual period, and the estimated date of delivery for estimating gestational age of the infant. You want to know about any chronic and acute conditions that occur during pregnancy such as diabetes, epilepsy, or infections. You want to know the timing and results of prenatal testing, both ultrasound and amniocentesis - when was the earliest ultrasound that was used for dating to assess gestational age, were</p>

	<p>there any ultrasounds that showed microcephaly or other kinds of brain anomalies. Often knowing that things were normal is informative as well. And then you want to know about any pregnancy complications such as placental abruption, as we talked about, and whether there were any specific maternal exposures to medications or mercury ingestion, for example.</p>
<p>Slide 22: Information to Collect – Continued</p>	<p>You certainly want to know the type of pregnancy outcome that occurred - was it a live birth or possibly a fetal death, and at what gestational age. Or was the pregnancy electively terminated and why. You want to record all measurements of the infant at birth - not just the head circumference, but the weight and the length at delivery, and at a later time if they're available. And again, you need to be sure to record the date and the child's age when those were taken. You need to know the gestational age that was assigned to the infant at delivery and the infant sex. And then any co-occurring birth complications, such as respiratory distress, sepsis, meningitis. [You should include] findings on the physical exam, including all major and minor defects - not just whether there was microcephaly, but were there other findings as well. You'd like to know the evaluations performed that assessed the microcephaly, the date they were done, and the results. So cranial ultrasounds, CT scans, MRI scans, for example, looking for brain calcifications, or other anomalies of the CNS. And then you want to look at subspecialty evaluations that happened - either consultations during the newborn hospitalization or at a later date among referrals for pediatric neurology, ophthalmology - many of the infants in Brazil have abnormal eye findings as well [as] retinal anomalies - genetics evaluation, and audiology. Again, infants in Brazil have also had significant hearing loss. So you want to pick up the results of the newborn hearing screening and then results of any genetic testing that's done, the karyotype, any microarrays, or FISH analyses.</p>
<p>Slide 23: Information to Collect – Continued</p>	<p>In terms of Zika virus testing, right now this testing can be done at CDC and a few of the state health labs. And so the results of those tests actually may not be in the medical record if they were sent elsewhere to be performed. But you want to look for testing of the maternal serum during pregnancy or after delivery, any testing of amniotic fluid that was done, testing of the cord blood taken at delivery or of the infant serum at a later time, or the cerebral spinal fluid if that was obtained after birth. You want to look for Zika virus RNA results obtained by reverse-transcriptase polymerase chain reaction (RT-PCR), and for Zika virus-specific immunoglobulin (Ig) M results and neutralizing antibody results as well. The immunoglobulin results from Zika virus can cross react with other viruses, most notably dengue and chikungunya. So results of neutralizing antibodies that are specific to Zika are important. And then if there were specimens taken from the placenta or the umbilical cord, these should be fixed in frozen tissue. But they can be looked at for Zika virus immunohistochemical staining and RNA by RT-PCR.</p>
<p>Slide 24: Information to Collect – Continued</p>	<p>It's also important to look for other information about other <i>in utero</i> virus infections. Testing of maternal serum during pregnancy or after delivery for virus specific IgM and IgG antibodies - and this includes the list we talked about earlier for toxoplasmosis, CMV, rubella, etcetera - any testing of the cord blood or the infant serum for virus specific immunoglobulins. And then you need to look for whether the infant's urine was cultured for CMV which can be grown from that specimen as well.</p>
<p>Slide 25: Assessing Prevalence</p>	<p>So, I wanted to talk a little bit about assessing prevalence, [and] what you do with the surveillance data when you've collected it. Typically the numerator for assessing birth defects prevalence includes all outcomes - live births, stillbirths twenty weeks or greater, and elective terminations at any gestational age. The denominator for most systems includes the total number of live births in the population because the contribution of stillbirths and terminations to that number is very small and it's difficult to obtain an accurate estimate of how many actually occur. Birth defects are very rare so prevalence is</p>

	usually estimated per one thousand or per ten thousand live births and there can be a fair amount of year-to-year variation due to the limited size of the total population and the rarity of individual defects. If you have data for a few years, it can provide you some indication of how much variation you'd expect to see going forward. The reported prevalence of microcephaly in the U.S. varies from two to twelve cases per ten thousand live births among the state based birth defects programs, so it can vary quite a bit in different areas depending on the methods of ascertainment you use, the sources you go to, and other factors. The goal of this surveillance is really to identify a very large increase in prevalence that might reflect an increase in Zika virus infection in the community or some other exposure and we would expect to see maybe a three- to five-fold or more increase with something like that happening.
Slide 26: Metropolitan Atlanta Congenital Defects Program	These are data from our birth defect surveillance program here in metro Atlanta for seventeen consecutive years. The total number live births went from thirty eight thousand to fifty six thousand during that period, and you can see that the number of microcephaly cases vary quite a bit as did the prevalence over those years. We had prevalence as low as 4.3 per ten thousand in year 4 and as high as 10.2 per ten thousand in year 9. So this gives you an idea of how much variation you may see. In order to identify an increase you really need to look for something much larger than this year-to-year variation.
Slide 27: Metropolitan Atlanta Congenital Defects Program- Microcephaly	This slide also looks at the data from Atlanta for 2007 to 2013. In this we looked at the total prevalence of microcephaly which was about almost 7.0 per ten thousand, and then we excluded the cases where there was a known cause - those with known <i>in utero</i> infection, those with other defects, those with chromosomal abnormalities or diagnosed clinical syndromes, etcetera, And [we] found that about two thirds of the microcephaly [cases] - about 4.0 per ten thousand - did not have a known cause. And it would be among that group that you would expect to see an increase if you had a new exposure or a new infection occurring in the population.
Slide 28: Assessing Prevalence	<p>So, one thing that's helpful to do with surveillance data for microcephaly is, just descriptively, to subdivide the cases into various groups. So, you can subdivide them by severity of the microcephaly - how many are known to have a head circumference less than [the] third percentile which is the primary case definition; how many are you capturing where their heads circumference is actually between [the] third and fifth percentile but they still have a diagnosis of congenital microcephaly; how many have a head circumference greater than fifth percentile or how many missing values do you have which is an important group to assess.</p> <p>And then you can also look at how many of them have known or documented causes- how many of the infants have chromosomal or genetic abnormalities, realizing that not every infant may have been tested for those, but how many do you know were; how many have syndromes or single gene disorders either definitely diagnosed or suspected by a geneticist; how many have evidence of an <i>in utero</i> infection, so a positive culture or positive antibody titers; how many are known to have been exposed to a teratogen, such as maternal alcohol or medications; and then how many have no documented cause. And then you can look at the relative proportion of those groups over time and see if they're changing at all.</p>
Slide 29: Prevalence of Congenital Microcephaly By Severity	So this is just a diagram that shows that [referring to Slide 28: Assessing Prevalence]. If you look at the severity of microcephaly, you can start with all cases which is the crude prevalence of microcephaly in the population. You can remove those that have possible microcephaly according to the case definition. You can have another group that are those with relative microcephaly, where the head circumference is greater than fifth percentile but is disproportional. You can have another group where the head circumference percentiles are not available, so you don't really know what the severity of the

	microcephaly was. And then you can have the two groups where the head circumference is less than third percentile, strictly meeting the case definition; and those where it's maybe third to fifth percentile, a little bit milder form. And look at those descriptively over time.
Slide 30: Prevalence of Microcephaly By Documented Cause	And then you can also divide them by whether there's a documented cause. So again, you start with all cases for the crude prevalence, remove those with microcephaly that's due to another malformation, such as a neural tube defect, or holoprosencephaly. And then you have a revised prevalence and you can divide that into those with a documented cause - the chromosomal abnormalities, the genetic syndromes, documented <i>in utero</i> infections, teratogens, etcetera - and those where there's not a document cause. So, depending on how comprehensive the medical record is and the setting where these evaluations are conducted, you may have children that you don't have access to any records that indicate a known cause. It's possible that one was found at later time and you just don't have access, so you have to consider those kinds of things as well.
Slide 31: Microcephaly and Zika	So, a little bit about microcephaly and Zika at this point. We know that there are a small number of positive test results for Zika virus infection in the infants in Brazil that have microcephaly. We know that the microcephaly pattern in some of these infants is consistent with the fetal brain disruption sequence, and that's based on photographs and scans of a small number of the infants. But it's also been described in a retrospective investigation of a Zika outbreak in French Polynesia, and it has been described in other types of intrauterine infection such as CMV. What we don't know is whether there really is a causal relationship between Zika virus and microcephaly or other adverse pregnancy outcomes. That's what's trying to be assessed definitively now. We don't know the full spectrum of phenotypes in infants that are affected whose mothers had Zika virus. So, there's a lot of focus on the infants with the severe microcephaly and the severe brain damage. But whether there might be a milder phenotype where the head size is not so small, or there are just lesser abnormalities of the brain, or they are simply developmental problems later on, or simply hearing loss without many other manifestations, we don't really know what that full spectrum is. We also don't know for certain the impact of timing of infection during pregnancy or the impact of the severity of mothers with infection. So, one would think that an infection that occurred early in pregnancy would lead to more severe damage in the fetus than one that occurred in the latter half of pregnancy or maybe in the third trimester. That makes sense, [but] we don't really have data on that yet, or whether the mothers who experienced symptoms of Zika virus have more severely affected infants than those who had a milder form where they didn't notice any symptoms. And then we don't really know the magnitude of the possible risk of microcephaly and other types of adverse outcomes following Zika virus infection. All of that is still trying to be determined.
Slide 32: Conclusion	So, in closing, I'd like to thank everyone who was part of putting these slides together and providing information. I want to refer people to the National Birth Defects Prevention Network website. We have a document posted there that goes over much of this material in a surveillance case definition for microcephaly. And then certainly follow the CDC Zika website which is updated continually as new information becomes available. Thank you.